## REMARKS

Prior to entry of the present amendment, claims 2-7, 10, 11, and 13-29 are pending. Claims 13-15 are rejected under 35 U.S.C. § 112, first paragraph, claims 28-29 are rejected under 35 U.S.C. § 112, second paragraph, claims 2-3, 10, 11, 16-19, 21, and 23-29 are rejected under 35 U.S.C. § 102, and claims 2-7, 10, 11, and 13-29 are rejected under 35 U.S.C. § 103. Applicants address each basis for rejection as follows.

### Information Disclosure Statement

Applicants note that two references submitted with the September 21, 2009 Information Disclosure Statement were crossed out on the Form PTO-1449 returned by the Office with the present Office Action. These references apparently were not considered by the Examiner because the Form PTO-1449 did not include the author's name. Applicants re-submitted the crossed out references with an Information Disclosure Statement filed on April 14, 2010 and included the author's name on the Form PTO-1449 filed with the April 14th Information Disclosure Statement. Applicants respectfully request consideration of the references.

### Claim Amendments

Claim 2 has been amended to require the "immature dendritic cell" to be a "$CD11c^+$" immature dendritic cell. Support for this amendment is found, for example, at page 16, lines 13-15, of the English specification. Here the specification states (emphasis added):

> In the present invention, it is preferable to mix a minus-strand RNA viral vector with a cell fraction containing a high density of dendritic cells or precursor cells thereof (for example, $CD11c^+$ cells or $CD34^+$ cells).

Claim 2 has also been amended to incorporate the features of claim 4, and claim 21 has been amended to incorporate the features of claim 22. In view of these amendments, claims 4 and 22 have been cancelled and the dependency of claim 5 has been amended.

Claims 11, 23, and 24 have been amended to clarify that the cell is $CD11c^+$. Claim 13 has been amended to recite that the dendritic cell is "syngenic or allogenic" to the subject to whom it is administered. Support for the amendment to claim 13 is found, for instance, in "Experiment 4" of the specification where allogenic or syngenic T cells were co-cultured with

dendritic cells.

Claims 3 and 26-29 have been cancelled and new claims 30-33, which are based on claims 3 and 26-29, have been added.

New claim 34 has been added and recites that the introduction efficiency of the Sendai virus vector into the immature dentritic cell or precursor cell of a dendritic cell is 70% or more. Support for this amendment is found, for example, at page 6, lines 10-12, of the English language specification, as well as in Figure 7.

No new matter has been added by the present amendments. Applicants reserve the right to pursue any cancelled subject matter in this or in a continuing application.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 13-15[1] are rejected under 35 U.S.C. § 112, first paragraph, on the basis of an asserted lack of enablement for the full scope of the claims. The Office states (pages 2 and 3; emphasis original):

> [T]he specification, while being enabling for: A method for suppressing tumor growth comprising the step of delivering **an autologous or allogeneic Sendari *[sic]* virus vector-containing mature dendritic cell to tumor site, wherein the mature dendritic cell was pulsed or primed with a tumor antigen**; does not reasonably provide enablement for a method for suppressing tumor growth as broadly claimed.

Applicants submit that the claims as amended are free of this basis for rejection.

In particular, claim 13 has been amended to require the dendritic cell to be syngenic or allogenic and now reads on delivering a vector-containing mature dendritic cell to a subject having a tumor, where the dendritic cell is syngenic or allogenic to the subject. Accordingly, Applicants submit that claim 13 as amended is directed to subject matter that the Office has indicated to be enabled by the application as filed.

Although the Office states that the mature dendritic cell needs to be pulsed or primed with a tumor antigen, Applicants note that the specification teaches that "[w]hen DC/SeV-GFP [dendritic cell/Sendai virus-green fluorescent protein] was used, significant anti-tumor effects

[1] Applicants submit that claim 15 has been included in this basis for rejection in error. Applicants address the rejection as it applies to claims 13 and 14.

could be observed, with the strongest tumor suppression being observed in mice treated with DC/LPS [dendritic cell/lipopolysaccharide] and mice treated with DC/SeV-IFNβ [dendritic cell/Sendai virus-interferon β]" (page 50, lines 33-35; emphasis added). In view of the teachings of the specification, Applicants submit that anti-tumor activity was exhibited by Sendai virus containing dendritic cells without pulsing or priming with a tumor antigen.

For the reasons set forth above, Applicants submit that the full scope of claim 13, as amended, and claim 14, which depends from claim 13, is enabled by the specification as filed. This basis for rejection may be withdrawn.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 28-29 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite. The Office states (page 6):

> [I]t is unclear what is encompassed by the term "the cell". Does the term refer to the cell that is contacted with Sendai virus vector?

Claims 26-29 have been replaced with new claims 30-33. New claims 30 and 31 require contacting the Sendai virus vector with the $CD11c^+$ immature dendritic cell, and claims 32 and 33 require contacting the Sendai virus vector with the $CD34^+$ or $CD11c^+$ precursor cell of a dendritic cell. Applicants submit that new claims 30-33 are free of the indefiniteness rejection.

Rejection under 35 U.S.C. § 102

Claim 21 is rejected under 35 U.S.C. § 102(b) as being anticipated by Jin et al. (Gene Therapy 10:272-277, 2003; "Jin") as evidenced by Romani et al. (J. Exp. Med. 180:83-93, 1994; "Romani"); claims 2-3, 10, 11, 19, 21, and 23-29 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gary-Gouy et al. (J. Interferon and Cytokine Res. 22:653-659, 2002; "Gary-Gouy"); and claims 11, 16-19, and 24 are rejected under 35 U.S.C. § 102(e) as being anticipated by Pickles et al. (US 2005/0048030 A1; "Pickles"). Applicants address each basis for the anticipation rejection as follows.

*Claim 21*

In rejecting claim 21 as being anticipated by Jin, the Office states that Jin "disclosed a

method in which recombinant Sendai virus is in contact and provides a highly efficient gene transfer into human cord blood CD34+ cells" and "$CD34^+$ cells are precursors of dendritic cells" as evidenced by Romani (Office Action, page 7). Claim 21 has been amended to include the features of claim 22. Claim 22 was not included in this basis for the anticipation rejection. Consequently, Applicants submit that claim 21, as amended, is free of the anticipation rejection over Jin as evidenced by Romani.

*Claims 2-3, 10, 11, 19, 21, and 23-29*

In rejecting claims 2-3, 10, 11, 19, 21, and 23-29 as being anticipated by Gary-Gouy, the Office states (page 8; emphasis added):

> Additionally, since CD11c+ myeloid dendritic cells taught by Gary-Gouy do not express markers such as CD80, CD83 and CD86 nor were they subjected to further stimulation by LPS; they fall within the scope of "immature dendritic cells" as defined by the present application (see at least page 10, lines 16-20; page 11, lines 14-19).

Applicants submit that the claims as amended are free of this basis for rejection.

Gary-Gouy does not teach $CD11c^+$ precursors of dendritic cells or $CD11c^+$ immature dendritic cells. In particular, Applicants note that Gary-Gouy fails to describe that the dendritic cells do not express markers such as CD80, CD83, and CD86. Instead, Gary-Gouy simply is silent about these matters. Gary-Gouy gives no information about the maturation stage of the dendritic cells used in the experiments. Applicants submit that the absence of information about the expression of the CD80, CD83, and CD86 markers cannot serve as evidence that these markers were not present. Accordingly, Applicants submit that Gary-Gouy does not describe "immature" dendritic cells as recited in the claims. Applicants submit that Gary-Gouy does not anticipate the presently amended claims.

*Claims 11, 16-19, and 24*

In rejecting Claims 11, 16-19, and 24 as being anticipated by Pickles, the Office states (page 9):

> Pickles et al teach at least a method for transferring a nucleotide sequence to a cell *in vitro* or *ex vivo* using a recombinant paramyxovirus vector, wherein the cell can

be a human dendritic cell (see at least paragraphs 122-130), the recombinant paramyxovirus vector includes Sendai virus vector (at least paragraphs 43-45) and the nucleotide sequence encodes a cytokine such as beta-interferon or a tumor antigen (paragraphs 86, 92-103).

For the following reasons, this basis for the section 102 rejection may be withdrawn.

The claims, as noted above, have been amended to recite "$CD11c^{+}$" dendritic cells. Pickles fails to describe such cells and, on this basis alone, cannot anticipate claim 11, and its dependent claims, as presently amended.

In addition, as argued in Applicants' last response (see, e.g., page 8 of the response filed on September 21, 2009), the disclosure of a reference that is asserted to be anticipatory must provide an enabling disclosure of the desired subject matter. Mere naming or description of the subject matter is insufficient.

Pickles uses only a few virus vectors (respiratory syncytial virus (RSV), adenovirus (AdV), and human parainfluenza virus type 3 (PIV3), etc.) in the experiments for transduction and only transduces airway epithelial cells. Pickles states (paragraph number in parentheses; bold original; underlining added):

> [0151]
> This showed that RSV preferentially targets the ciliated cells of the airway epithelium, and that infection (and subsequent virus release) occurs exclusively via the apical surface.
>
> [0163]
> . . . whereas inoculation of the basolateral surface resulted in little or no infection (**FIG. 3**).
>
> [0164]
> These results show that rgRSV efficiently infects WD HAE cells via the apical but not the basolateral surface, which is the direct inverse of the polarized gene transfer characteristics of AdV.
>
> [0166]
> Basolateral inoculation of rgRSV resulted in little or no GFP expression in any cell type within the epithelium (<0.01% of cells). In contrast, parallel studies with AdVGFP revealed an absence of GFP expression following inoculation of the apical surface, . . .

[0170]
We and others have previously shown that the apical surfaces of WD HAE cultures are resistant to AdV-mediated gene transfer because the receptors required for AdV entry are absent from the apical surfaces of airway epithelia . . .

PD HAE cultures that were inoculated with rgRSV had no evidence of GFP expression 24 to 48 h later (data not shown), indicating that these cells are not susceptible to rgRSV infection.

[0180]
No GFP expression was observed in cultures inoculated via the basolateral surface . . .

[0181]
Laser scanning confocal microscopy was used to generate optical sections of hPIV3GFP infected cultures and revealed that hPIV3GFP infected cells were exclusively lumen-facing ciliated columnar epithelial cells . . .

[0184]
In contrast, EIAV pseudotyped with vesicular stomatitis virus protein G (VSV-G) only transduced from the basolateral surface.

The Examples described in Pickles strongly suggest that the susceptibility of a cell to the virus varies from virus to virus. Some viruses infect the cell from the basolateral surface, but others do not. Applicants submit that, unless a working example is provided, it is unpredictable whether or not a particular virus infects a particular cell. Pickles only uses airway epithelial cells in combination with a limited number of virus vectors. Pickles fails to use Sendai virus or dendritic cells in any of the experiments described in the Examples. Applicants submit that, given Pickles, the person of ordinary skill in the art would not have been able to determine which cell is susceptible to which virus without undue experimentation, because the Examples of Pickles suggest that the susceptibility of a cell to the virus would vary significantly from virus to virus. Therefore, Applicants submit that the person of ordinary skill in the art would not take the description of paragraphs of Pickles relied on by the Office (paragraphs 43-45, 86, 92-103, and 122-130) as an enabling disclosure. For all the above reasons, Applicants submit that Pickles does not anticipate the claims as presently amended.

Rejection under 35 U.S.C. § 103

Claims 2-7, 10, 11, 13-14, and 13-29 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Song et al. (US 2002/0123479 A1; "Song") in view of Tokusumi et al. (US 6,746,860 B1; "Tokusumi"), Jin, Hwu et al. (US 6,734,014 B1; "Hwu"), and Waller et al. (US 2005/0013810 A1; "Waller"). Applicants respectfully traverse this basis for rejection.

Applicants, in the last reply, argued that an anticipating reference must provide an enabling disclosure of the subject matter relied upon in making the rejection and that Song fails to meet this standard. In particular, Applicants noted that Song only provides results of gene introduction into dendritic cells using a retrovirus vector and that one skilled in the art would not reasonably conclude that *any* recombinant negative strand RNA virus could be used without undue experimentation because no working example using a virus vector other than a retrovirus vector is provided. In response, in the present Office Action, the Office states (pages 11 and 12; underlining original, bold added):

> **Within the scope of enablement, Song et al disclose** compositions and methods useful for stimulating an immune response against one or more disease associated antigens, including cancer associated antigens, by genetically modifying dendritic cells including dendritic progenitor cells as well as dendritic cells having CD11c+ maker, *in vivo* or *ex vivo*, wherein the dendritic cells were genetically modified by **a recombinant negative strand RNA virus (e.g., vesicular stomatitis virus, paramyxoviruses, orthomyxoviruses and bunyaviruses)** directing the expression of at least one disease associated antigen (see at least Summary of the Invention; particularly paragraphs 6-7, 9-12, 16-18, 41-45, 60 and Figure 1).
>
> * * *
>
> Song et al did not teach explicitly the use of a Sendai virus vector for genetically modifying immature dendritic cells, including dendritic progenitor cells, even though **they disclosed that dendritic cells, including dendritic progenitor cells could be genetically modified by any recombinant negative strand RNA virus including any paramyxovirus**; nor did Song et al teach specifically the use of CD34+ dendritic precursor cells or the step of further culturing the CD34+ precursor cells with GM-CSF and IL-4.

In view of the above citations, Applicants submit that the Office has taken the position that Song discloses, within the scope of enablement, that dendritic cells could be genetically modified by

any recombinant negative strand RNA virus. Applicants submit that this position is unfounded in view of the Office's own cited reference, Gary-Gouy.

Gary-Gouy is a reference newly relied on by the Office in the present Office Action in making the anticipation rejection discussed above. In particular, Gary-Gouy describes plasmacytoid dendritic cells ($CD123^+$ $CD11c^-$) (PDC) and $CD11c^+$ myeloid dendritic cells (MDCs) incubated with Sendai virus (SV). Gary-Gouy states that "PDC produced large amounts of IFN-I after HSV infection and also after infection with SV" (page 655, left column, second paragraph, lines 16-18). However, Gary-Gouy also states that "$CD11c^+$ MDC **failed** to produce significant amounts of IFN-I under any of the conditions" (page 655, left column, second paragraph, lines 14-15; emphasis added). Gary-Gouy further states that "[t]he lack of production by our sorted MDC might reflect **their incapacity** to internalize SV particles" (page 658, left column, lines 3-5; emphasis added). These descriptions clearly indicate that Gary-Gouy failed to introduce Sendai virus into $CD11c^+$ MDCs. Gary-Gouy also states that "mature MDC have been shown to be potent IFN-I producers after infection with influenza virus" (page 658, left column, lines 1-3). In short, Gary-Gouy teaches that infection of $CD123^+$ $CD11c^-$ plasmacytoid dendritic cells (PDC) with Sendai virus was successful, but infection of $CD11c^+$ myeloid dendritic cells (MDC) with Sendai virus was unsuccessful, although infection with influenza virus is known to be successful.

In view of Gary-Gouy, Applicants submit that the Office's position that Song discloses, within the scope of enablement, that dendritic cells could be genetically modified by any recombinant negative strand RNA virus, is not in accordance with the knowledge in the art. Gary-Gouy suggests that infectivity of dendritic cells can vary greatly between different types of viruses. Applicants submit that Song fails to provide an enabling disclosure for even one negative strand RNA virus because Song provides no experimental results using a negative strand RNA virus. In contrast, Gary-Gouy suggests that infectivity of dendritic cells can vary between viruses and shows that infection of $CD11c^+$ myeloid dendritic cells (MDC) with Sendai virus was unsuccessful (see, e.g., page 655, left column, second paragraph, lines 14-15).

The Office combines the teachings of Song with those of Tokusumi, Jin, Hwu, and Waller. However, the cited supplemental references do not make up for the lack of a reasonable

expectation of success, because none of the additional references describes a dendritic cell transduced with a negative strand RNA virus, whereas the finding of Gary-Gouy suggests that the gene transfer to dendritic cells would be unpredictable. Hence, in view of the lack of success described in Gary-Gouy, combining Song, Tokusumi, Jin, Hwu, and Waller would not lead one skilled in the art to have to a reasonable expectation of successfully introducing a Sendai virus into dendritic cells. On this basis alone, Applicants submit that the presently claimed invention is nonobvious over the combination of the cited art. The present rejection under 35 U.S.C. § 103 should be withdrawn.

For the sake of completeness, Applicants also wish to address various statements made by the Office in the present Office Action.

The Office states (page 11; underlining original; bold added):

> Since the starting dendritic cells (including both dendritic cells and dendritic progenitors) used by Song et al **do not express markers such as CD80, CD83 and CD86** (see at least Figure 1 for cellular dendritic cell markers taught by Song et al; paragraphs 9, 41-44), they fall within the scope of "immature dendritic cells" as defined by the present application (see at least page 10, lines 16-20; page 11, lines 14-19).

In response, as explained above, Applicants submit that the absence of information of whether a particular marker was expressed or not is not equivalent to a teaching that the marker was not expressed. In Figure 1 of Song, if the gene is not expressed in dendritic cells, it is clearly indicated by a "(-)" symbol, and Song states that "[m]arkers indicated with a (-) are not present on dendritic cells" (paragraph [0019], lines 2-3). Song is silent about whether CD80, CD83, or CD86 is expressed on dendritic cells. The Office's conclusion that Song teaches that CD80, CD83, and CD86 are not expressed on the cells used by Song does not follow from the data presented in Song. Song simply is silent on whether or not these markers are expressed.

In response to Applicants' last reply, the Office states (page 16; underlining original, bold added):

> Firstly, the above rejection is made under 35 U.S.C. 103(a) and therefore there is no requirement that the primary Song et al reference has to teach the use of a Sendai virus vector, let alone demonstrating specifically transfection of a precursor of a dendritic cell (e.g., CD34 cells) with a Sendai virus vector.

> Nevertheless, **Song et al taught** specifically compositions and methods useful for stimulating an immune response against one or more disease associated antigens, including cancer associated antigens, by genetically modifying dendritic cells including dendritic progenitor cells, *in vivo* or *ex vivo*, wherein the dendritic cells were genetically modified by **a recombinant negative strand RNA virus** (e.g., vesicular stomatitis virus, paramyxoviruses, orthomyxoviruses and bunyaviruses) directing the expression of at least one disease associated antigen. At the effective filing date of the present application, **the teachings of Song et al are enabled as evidenced at least by** the teachings of Jin et al, Li et al, Steinman et al, and **Gary-Gouy et al** as discussed further below. Furthermore, the teachings of Song et al are not limited only to preferred embodiments; and therefore there is no "teaching-away" whatsoever by the Song reference as argued by Applicants.

As argued in the last response, Applicants maintain that gene transfer to dendritic cells with a recombinant negative strand RNA virus is not "taught" in Song, because Song only provides experiments using a retrovirus vector. While the Office asserts that the teachings of Song are enabled as evidenced by the references including Gary-Gouy, Applicants submit that Gary-Gouy failed to introduce Sendai virus to the $CD11c^+$ myeloid dendritic cells (MDCs) (see page 655, left column, second paragraph, lines 14-15, and page 658, left column, lines 3-6 of Gary-Gouy). Clearly Gary-Gouy does not support the contention that Song is enabling for the introduction of Sendai virus into $CD11c^+$ cells as recited in the presently amended claims.

Applicants also direct the Office's attention to the reply filed on December 5, 2008, where Applicants argued that the transgene expression was very high when the Sendai virus vector was used to infect immature dendritic cells, which was in contrast to the result obtained when the Sendai virus vector was used to infect to mature dendritic cells (see pages 10-11 of the December 5, 2008 reply and Fig. 9(B) of the specification.). Applicants note that Gary-Gouy not only fails to describe this difference, but also Gary-Gouy fails to introduce the vector into $CD11c^+$ immature dendritic cells or precursors of dendritic cells.

The Office further states (pages 16 and 17; original emphasis deleted and new emphasis added):

> Secondly, in contrast to Applicant's position that highly efficient gene transduction to immature dendritic cells or dendritic precursor cells such as CD34 stem cells by Sendai virus vector was unpredictable at the effective filing date of the present application, the teachings of Jin et al cited in the above rejection indicated otherwise. Furthermore, Li et al (J. Virol. 74:6564-6569, 2000; IDS) also demonstrated that a Sendai virus vector mediated a gene transfer and

expression in various types of animal and human cells, including non-dividing cells, with high efficiency (see at least the abstract).

In response, Applicants submit that neither Jin nor Li describes dendritic cells containing a Sendai virus vector. Even if gene transfer in some types of "animal and human cells including non-dividing cells" was shown to be successful by Jin or Li, Gary-Gouy was unsuccessful in infecting $CD11c^+$ dendritic cells with Sendai virus. Considering the failure of Gary-Gouy using the cell type recited in the presently amended claims, Applicants submit that the Office has failed to establish that successful transduction of dendritic cells, let alone with Sendai virus, was predictable.

The Office also states (page 17; emphasis original):

> Thirdly, at the effective filing date of the present application **Steinman et al (US 6,300,090) already successfully transfecting proliferating or non-proliferating human dendritic cells (both mature and non-mature cells) with at least a recombinant influenza viral vector which is minus-strand RNA viral vector that belongs to the same family as Sendai virus vector (see at least issued claims of US 6,300,090).** Furthermore, **Gary-Gouy et al already demonstrated that plasmacytoid dendritic cells (CD123+CD11c-) and CD11c+ myeloid dendritic cells as well as peripheral blood monocytes from human blood donors were infected readily by a Sendai virus** (see at least the sections titled "Cell purification" and "Type 1 IFN assay" on page 654 and the section titled "Monocytes and CD123hi PDC but not CD11c+ MDC produce IFN-1 on specific stimulation" on page 655).

Applicants do not dispute the Office's assertion that Steinman succeeded in transfecting proliferating or non-proliferating human dendritic cells using a recombinant influenza viral vector, which is a minus-strand RNA viral vector that belongs to the same family as a Sendai virus vector. Applicants also agree that Gary-Gouy describes that "mature MDC have been shown to be potent IFN-I producers after infection with influenza virus" (page 658, left column, lines 1-3; emphasis added). Nevertheless, Gary-Gouy failed to introduce Sendai virus into $CD11c^+$ myeloid dendritic cells (MDCs) (see page 655, left column, second paragraph, lines 14-15, and page 658, left column, lines 3-6). Applicants submit that, in contrast to the Office's assertion, the findings of Gary-Gouy demonstrate the unpredictability of gene modification of dendritic cells. In particular, contrary to the Office's assertion that "Gary-Gouy et al already demonstrated that . . . CD11c+ myeloid dendritic cells . . . were infected readily by a Sendai

virus" (Office Action, page 19, emphasis removed), as explained above, Gary-Gouy was unsuccessful in infecting $CD11c^+$ dendritic cells with Sendai virus. Applicants submit that nothing in Steinman, which describes use of a recombinant influenza virus vector, would cause the skilled artisan to reconsider that the ability of a Sendai virus vector to infect $CD11c^+$ dendritic cells is unpredictable in view of the findings in Gary-Gouy.

Further, the Office states (page 17):

> Fourthly, the instant claims do not require any particular transfection efficiency and the combined teachings Song et al., Tokusumi et al., Jin et al., Hwu et al. and Waller et al. as set forth in the above rejection meet all the limitation of the claims as written.

In response, Applicants again note that transfection efficiency is a required outcome for carrying out the claimed invention. The office personnel looks not only to the subject matter which is literally recited in the claim in question ... but also to those properties of the subject matter which are inherent in the subject matter *and* are disclosed in the specification (See M.P.E.P. § 2141.02(V); italics original; underlining added). As such, the efficiency is relevant even though a particular efficiency is not recited in the claims. Claim 2 recites the feature that the "immature dendritic cell of (i) or (ii) undergoes maturation thereby producing a mature dendritic cell." This feature is neither taught nor suggested by the cited prior art, even if combined.

The Office states (page 17; emphasis added):

> Fifthly, it should be noted that the state of the prior art at the filing date of the present application was not defined exclusively by the teachings of the Cramer *[sic]* reference cited by Applicants. Once again, please refer at least to all of the teachings of the cited prior art used in the rejections of record.

In response, Applicants submit that the cited art of record, not just Cremer (Hum. Gene Ther. 11(12):1695-1703, 2000; "Cremer"), supports Applicants' contention that the efficient transduction of a dendritic cell with a Sendai virus vector was unpredictable. On this point, Applicants refer to the below citations from Cremer and three references cited by the Office (Song, Hwu, and Gary-Gouy).

Cremer teaches that "[b]eing averages, these values . . . may mean that <25 or 30% of the cells were transduced" (page 1697, right column, second paragraph, lines 8-10; emphasis added).

Song describes that "[h]ere, 0.2% of dendritic cell fractions were transduced..."

(paragraph [0173]; emphasis added). Song also describes that "[o]n the basis of retrovirus-mediated luciferase expression, transduction efficiency of dendritic cells was approximately 0.1% via identical protocol followed by normalization based on protein content" (paragraph [0177]; emphasis added). Song further describes that "the retroviral vector transduction efficiency was estimated to be only 1%" (paragraph [0259]; emphasis added).

Hwu describes that "25-30% of B7-2+ dendritic cells expressed the marker gene on FACS analysis" (column 30, lines 13-14; emphasis added).

Gary-Gouy describes that "$CD11c^+$ MDC failed to produce significant amounts of IFN-I under any of the conditions" and "[t]he lack of production by our sorted MDC might reflect their incapacity to internalize SV particles" (page 655, left column, second paragraph, lines 14-15, and page 658, left column, lines 3-6, respectively; emphasis added).

In contrast to the cited art, Applicants' specification teaches that immature dendritic cells are very efficiently infected with Sendai virus (82.2 to 95.4%, see values in upper right quadrant of each panel of Fig. 7). Applicants submit that, when inclusively considering the prior art, the significance of the high infection efficiency of immature dendritic cells by Sendai virus is quite apparent. Applicants maintain that this finding was unexpected over the cited art.

At page 18, the Office states:

> Firstly, the examiner notes that Applicants appear to consider each of the cited references in total isolation one from the others; and this is improper. As already pointed above, the above rejection is made under 35 U.S.C. 103(a) and therefore none of the cited references has to teach every elements of the claims.

In response, Applicants note that none of Song, Hwu, and Waller provides a working example using Sendai virus vector, and none of Tokusumi and Jin provides a working example using dendritic cells. While Applicants do not dispute that, for the purpose of 35 U.S.C. § 103, none of the references alone has to teach every element of the claims, there must have been at least a reasonable expectation of success in combining the teachings of the references to arrive at the claimed invention. Applicants submit that the references as combined by the Office fail to render the presently claimed invention obvious.

Gary-Gouy (cited by the Office) teaches that plasmacytoid dendritic cells produced large amounts of IFN-I after infection with Sendai virus (see page 655, left column), but it also teaches

that CD11c$^+$ myeloid dendritic cells failed to produce significant amounts of IFN-I after contact with Sendai virus (see, page 655, left column, second paragraph, lines 14-15). Both of CD11c$^-$ plasmacytoid dendritic cells and CD11c$^+$ myeloid dendritic cells are dendritic cells, but the results obtained using these two types of dendritic cells are very different. Clearly, even within types of dendritic cells, the infectivity of Sendai virus can be very different. Given this variability, Applicants submit that combining the Song, Hwu, and Waller references with Tokusumi and Jin would not yield a reasonable expectation of success, because neither Tokusumi nor Jin provides even one experiment using dendritic cells. The successful infection of CD11c$^+$ dendritic cells by Sendai virus is not rendered obvious by the cited art, even if combined.

Applicants' specification also teaches that high susceptibility of CD11c$^+$ myeloid dendritic cells to Sendai virus infection is only observed in immature state (see Fig. 9). Namely, even within CD11c$^+$ myeloid dendritic cells, the infectivity dramatically changes depending on its maturation state. None of cited references describes or suggests this finding. In particular, Gary-Gouy was unsuccessful in using Sendai virus to obtain transfected CD11c$^+$ myeloid dendritic cell, and, therefore, if anything, teaches away from use of Sendai virus to infect CD11c$^+$ dendritic cells.

Gary-Gouy further teaches that mature myeloid dendritic cells are potent IFN-I producers after infection with influenza virus but not with Sendai virus. As the Office states, influenza virus is a minus-strand RNA virus that belongs to the same family as Sendai virus. Here, Gary-Gouy supports the contention that, even within minus-strand RNA viruses, infectivity can be very different among the viruses.

The Office states (pages 18 and 19; emphasis added):

> Secondly, with respect to the issue of unreasonable expectation of success that Sendai virus could be transduced into CD34+ cells without disturbing differentiation of the cells into dendritic cells and/or Sendai virus vector into dendritic cells as argued by Applicants; please refer at least to the teachings of Steinman et al (US 6,300,090), Gary-Gouy et al (J. Interferon and Cytokine Res. 22:653-659, 2002; IDS) and Hwu et al (US 6,734,014). There was no evidence from any of these teachings that Sendai virus, retrovirus or any other viral vector would adversely affect the differentiation of dendritic precursor cells, including CD34+ precursor cells, into dendritic cells.

In response, Application submit that none of the cited references gives insight into what would happen when $CD34^+$ cells containing Sendai virus were to be subjected to differentiation into dendritic cells. The Office directs Applicants' attention to Steinman, Gary-Gouy, and Hwu. However, Steinman only teaches the results of influenza virus infection, and as explained above, Gary-Gouy teaches that the results obtained using influenza virus and Sendai virus were disparate. Furthermore, Gary-Gouy failed to introduce a Sendai virus vector into the $CD11c^+$ myeloid dendritic cells. Consequently, Applicants submit that, in view of the art, there would have been no reasonable expectation that the Sendai virus vector can be efficiently transduced to immature dendritic cells. Furthermore, as explained above, Applicants observed high expression from the Sendai virus vector in dendritic cells even after the cells were matured, although the matured cells were no more susceptible to the infection (see Fig. 9 of the specification). This result was also unpredictable. The third reference, Hwu, does not remedy the deficiencies of Steinman and Gary-Gouy because it does not describe use of even one negative strand RNA virus.

The Office asserts that there was no evidence that Sendai virus would adversely affect the differentiation of dendritic cells. As pointed out above, the lack of information is nothing more than lack of information. The present inventors have shown that immature dendritic cells infected with Sendai virus undergo spontaneous maturation. Namely, Sendai virus indeed affects differentiation of the cells. Consequently, Sendai virus might also affect the cell state during the differentiation from $CD34^+$ cell to dendritic cells. Although the finding of the present invention is not the prior art, it provides insight into considering whether the success of differentiation into immature dendritic cells was reasonably expected or not.

The Office states (page 19; original emphasis deleted):

> Furthermore, Steinman et al already successfully transfecting proliferating or non-proliferating human dendritic cells (both mature and non-mature cells) with at least a recombinant influenza viral vector which is [a] minus-strand RNA viral vector that belongs to the same family as Sendai virus vector; and Gary-Gouy et al already demonstrated that plasmacytoid dendritic cells (CD123+CD11c-) and CD11c+ myeloid dendritic cells as well as peripheral blood monocytes from human blood donors were infected readily by a Sendai virus . . .

Applicants respectfully disagree with these statements. As noted above, Gary-Gouy failed to introduce Sendai virus into $CD11c^+$ myeloid dendritic cells. Gary-Gouy also teaches that the result of $CD11c^+$ myeloid dendritic cells is different from that of plasmacytoid dendritic cells even though both cells are dendritic cells. Gary-Gouy further teaches that the result of Sendai virus is different from that of influenza virus even though these two viruses belong to the same family.

The Office states (page 19):

> Thirdly, with respect to the issue that CD34+ cells infected with Sendai virus are not the claimed subject matter; please refer at least to claims 2, 4-5, 20-21 of the present application.

In response, Applicants confirm that $CD34^+$ cells infected with Sendai virus are encompassed by some of the pending claims.

The Office further states that "Applicant's position [is] that highly efficient gene transduction to . . . dendritic precursor cells such as CD34 stem cells by Sendai virus vector was unpredictable at the effective filing date of the present application . . ." (Office Action, page 16). However, this is not Applicants' position.

Applicants wish to clarify that Applicants' position is that the success of differentiation from $CD34^+$ cells carrying Sendai virus to immature dendritic cells was unpredictable, because Sendai virus affects the differentiation state of the cells as shown at page 46, line 30, to page 47, line 3, of the present specification. Applicants' position is also that the high expression of Sendai virus vector observed in matured dendritic cells was unpredictable, because matured dendritic cells are insusceptible to infection with Sendai virus vector as shown in Fig. 9 of the present specification. Further, Applicants' position is that the spontaneous maturation of the dendritic cells having Sendai virus was unpredictable.

The Office, at page 20, states (emphasis original):

> Firstly, as already noted in the above rejection the methods and compositions resulted from the combined teachings of Song et al., Tokusumi et al., Jin et al., Hwu et al and Waller et al **are indistinguishable** from the methods and compositions as claimed by the present application. **Moreover, the spontaneous stimulation of immature dendritic cells to mature dendritic cells which are defined as dendritic cells having high expression of CD80, CD83 and CD86 is the "intrinsic property" of a Sendai virus.** Therefore, this intrinsic property of

> a Sendai virus would occur in the methods and compositions resulted from the combined teachings of Song et al., Tokusumi et ai., Jin et al., Hwu et al and Waller et al; regardless whether any of these inventors are aware of. This is also an evidence that **the above 103 rejection was not** based on hindsights and/or reconstructed based on the specification of the present application.

Applicants submit that the Office appears to consider the combination of the prior art references in total isolation from the fact that the Office has combined the prior art references. Even if the unexpected result is an intrinsic property of the combination, the combination itself is not an intrinsic property of the prior art. The combination was made by the Office with knowledge of the presently claimed invention.

The Office's assertion that, in essence, the method claims are unpatenable because "the mechanism of action of the instant method ... should be inherent" is unavailing because this is an inappropriate standard for obviousness. As held by the Federal Circuit, "[i]nherency and obviousness are distinct concepts." *W. L. Gore & Associates v. Garlock, Inc.*, 721 F.2d 1540, 1555, 220 U.S.P.Q. 303, 314 (Fed. Cir. 1983) (*citing In re Spormann*, 363 F.2d 444, 150 U.S.P.Q. 449, 452 (1966)), *cert. denied*, 469 U.S. 852, 105 S.Ct.172 (1984). *See also In re Oelrich*, 666 F.2d 578, 581-82, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981) ("The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency.]") (citations omitted) (emphasis added); and *In re Spormann*, 363 F.2d 444, 448, 150 U.S.P.Q. 449, 452 ("That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown."). The Office's retrospective view of inherency of the claimed invention is not a substitute for a teaching or suggestion supporting an obviousness rejection.

The Office states (page 21; emphasis removed):

> Secondly, with respect to new claims 25-29 it is further noted that the transfected dendritic cells taught by Song et al were not further subjected to any additionally *[sic]* treatment such as LPS stimulation for high expression of matured dendritic cell markers of CD80, CD83 and CD86.

Applicants note that the dendritic cells made in Song have a retrovirus vector which does not induce spontaneous maturation, whereas the claimed dendritic cells have a Sendai virus vector which, as taught by the specification, induces spontaneous maturation. Thus, there are clear

differences between the teachings of Song and viral vectors encompassed by the presently claimed invention.

Provisional Nonstatutory Obviousness-Type Double Patenting

Claims 11, 13-19, and 23-24 are provisionally rejected on the ground on nonstatutory obviousness-type double patenting over claims 1, 3-6, and 8-14 of co-pending application serial number 11/630,532 ("the '532 application).

Applicants again note that the present application, filed May 3, 2006, is the U.S. national stage of a PCT international application filed on October 29, 2004, whereas the '532 application, filed December 21, 2006, is the U.S. national stage of a PCT international application filed on April 28, 2005. Applicants submit that the present application, relative to the '532 application, is the earlier filed application. As such, in accordance with M.P.E.P. § 804, if the provisional obviousness-type double patenting rejection is the last remaining rejection in the present case, Applicants respectfully request that this provisional rejection be withdrawn and the application allowed to issue.

## CONCLUSION

Applicants submit that the application is now in condition for allowance, and such action is hereby respectfully requested.

Enclosed is a Petition to extend the period for replying to the Office Action for three (3) months, to and including May 5, 2010, and an authorization to charge the required extension fee to Deposit Account No. 03-2095.

If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: 28 April 2010

Jan N. Tittel, Ph.D.
Reg. No. 52,290

Clark & Elbing LLP
101 Federal Street
Boston, MA 02110
Telephone: 617-428-0200
Facsimile: 617-428-7045